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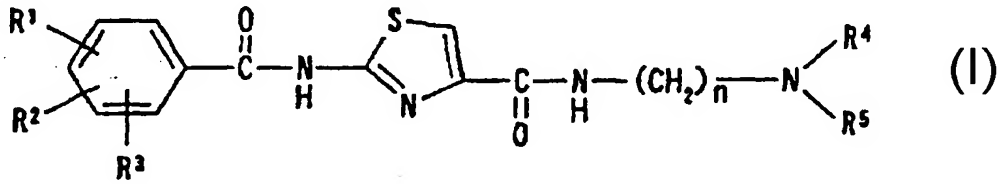
(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING AMINOTHIAZOLE DERIVATIVES FOR THE TREATMENT OF COLONIC MOTOR DYSFUNCTIONS



(I)

(57) Abstract: Remedies effective for the improvement of colonic motor dysfunction such as irritable bowel syndrome, constipation or intestinal atony without causing side effects on the central nerve system. These colonic motor dysfunction remedies comprise, as active ingredients, aminothiazole derivatives represented by the following formula (I) or a salt or hydrate thereof: wherein R^1, R^2 and R^3 may be the same or different and each independently represent a hydrogen atom or a hydroxyl, lower alkyl, lower alkoxy, amino, nitro or cyano group, R^4 and R^5 may be the same or different and each independently represent a hydrogen atom or a lower alkyl group, and n stands for an integer of from 2 to 4.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PHARMACEUTICAL COMPOSITIONS CONTAINING AMINOTHIAZOLE DERIVATIVES FOR THE TREATMENT OF COLONIC MOTOR DYSFUNCTIONS

Technical Field

This invention relates to remedies for colonic motor dysfunction, and more specifically to colonic motor dysfunction remedies comprising aminothiazole derivatives as active ingredients. This invention is also concerned with a treatment method for colonic motor dysfunction.

Background Art

From the anatomical viewpoint, the digestive tract is divided roughly into an upper digestive tract and a lower digestive tract. The upper digestive tract includes the esoplagus, the stomach and the duodenum, while the lower digestive tract includes the small intestine, the large intestine and the rectal. To diseases and symptoms which occur in the respective regions, treatments are applied correspondingly.

Illustrative of diseases of the upper digestive tract are diseases in the esophageal region, such as esophageal carcinoma, esophagostenosis and reflux esophagitis; diseases in the gastric region, such as gastric ulcer, gastritis and gastric cancer; diseases in the duodenal region, such as duodenal ulcer and

duodenal cancer; and as diseases occurring commonly in the gastric region and duodenal region, NUD (Non-Ulcer Dyspepsia) and gastroduodenal motor dysfunction. Examples of symptoms of such diseases of the upper digestive tract with which gastroduodenal motor dysfunction is associated include epigastric malaise, nausea, vomitting, brash, anorexia, bellyache, and dilatation of the stomach.

Illustrative of diseases of the lower digestive tract are colon cancer, colon polyp, ulcerative collitis, Crohn's disease, irritable bowel syndromes, constipation, intestinal atony, and drug-induced motor dysfunction. Of these, irritable bowel syndromes, constipation, intestinal atony and drug-induced motor dysfunction are diseases attributable to motor dysfunction of the large intestine, and are known to develop a cathartic disorder, such as constipation or diarrhea, and/or bellyache. Drug-induced motor dysfunction, on the other hand, is known to occur as a result of use of a calcium antagonist, a psychotropic or an antidepressant [Cardiology, **89**(suppl. 1), 10-15, 1998; J. Clin. Psychopharmacol., **19**, 401-406, 1999; Pharmacotherapy, **11**, 179-195, 1991].

As improvers for irritable bowel syndromes, trimebutine maleate, allosetron hydrochloride and tegaseroid maleate are known. Of these, trimebutine maleate has been found to give side effects on the central nerve system (sleep, dizziness and the like) via opioid receptors. With respect to allosetron

hydrochloride and tegaseroid maleate which are effective for diarrheal IBS and constipated IBS, respectively, there is an outstanding concern about side effect of constipation as an excess effect because drug efficacy is developed via serotonin receptors.

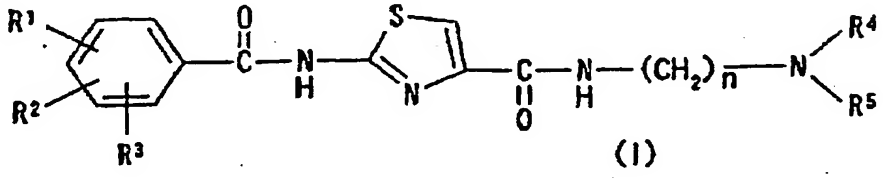
As gastroprokinetic agents for the upper digestive tract, cisapride, metoclopramide, itopride hydrochloride, mosapride citrate and the like are known (Gastroenterology, **118**, S32-S47, 2000). However, these improvers have been reported to be ineffective for constipation associated with irritable bowel syndromes which are diseases caused by colonic motor dysfunction (J. Clin. Pharmacol., **19**, 617-625, 1979; Scand. J. Gastroenterol., **33**, 128-131, 1998; Aliment. Pharmacol. Ther., **11**, 387-394, 1997).

PCT International Publications WO96/36619 and WO98/17654 disclose that aminothiazole derivatives enhance gastric motor activity and improve epigastric malaise, nausea, vomitting, brash, anorexia, bellyache, and dilatation of the stomach. These publications, however, make no mention about improving effects on diseases of the lower digestive tract caused by colonic motor dysfunction.

There is, accordingly, an outstanding desire for the development of improvers for colonic motor dysfunction, which are free of such side effects as those observed on the conventional irritable bowel syndrome improvers and caused via opioid receptors or serotonin receptors.

Disclosure of the Invention

The present invention provides a colonic motor dysfunction remedy comprising, as an active ingredient, an aminothiazole derivative represented by the following formula (I) or a salt or hydrate thereof:



(I)

wherein R^1, R^2 and R^3 may be the same or different and each independently represent a hydrogen atom or a hydroxyl, lower alkyl, lower alkoxy, amino, nitro or cyano group, R^4 and R^5 may be the same or different and each independently represent a hydrogen atom or a lower alkyl group, and n stands for an integer of from 2 to 4.

The present invention also provides use of an amino-thiazole derivative represented by the formula (I) or a salt or hydrate thereof for the production of a colonic motor dysfunction remedy.

The present invention also provides a treatment method for colonic motor dysfunction, which comprises administering an effective amount of an aminothiazole derivative represented by the formula (I) or a salt or hydrate thereof.

Best Modes for Carrying Out the Invention

In the aminothiazole derivative (I) useful in the practice of the present invention, the term "lower alkyl" means a linear, branched or cyclic, saturated hydrocarbon group which preferably has 1 to 6 carbon atoms. On the other hand, the term "lower alkoxy" means a group formed of a linear, branched or cyclic, saturated hydrocarbon, which preferably has 1 to 6 carbon atoms, and an oxygen atom bonded to the hydrocarbon.

Accordingly, illustrative of the "lower alkyl group" as R^1, R^2, R^3, R^4 and R^5 are linear, branched or cyclic alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, pentyl, 1-methylbutyl, 2-methylbutyl, isopentyl, tert-pentyl, 1,2-dimethylpropyl, neopentyl, 1-ethylpropyl, cyclopentyl, hexyl, 1-methylpentyl, 2-methyl-pentyl, 3-methylpentyl, isohexyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-methyl-1-ethylpropyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, and cyclohexyl. Among these, more preferred lower alkyl groups are linear or branched alkyl groups having 1 to 4 carbon atoms. Particularly preferred as R^4 and R^5 is isopropyl. Particularly preferred as R^1, R^2 and R^3 are H, hydroxy, methoxy, amino, nitro and cyano.

Illustrative of the "lower alkoxy group" as R^1, R^2 and

R^3 are linear, branched or cyclic alkoxy groups having 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, cyclopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, cyclobutoxy, pentoxy, 1-methylbutoxy, 2-methylbutoxy, isopentoxy, tert-pentoxy, 1,2-dimethylpropoxy, neopentoxy, 1-ethylpropoxy, cyclopentoxy, hexyloxy, 1-methylpentoxy, 2-methylpentoxy, 3-methylpentoxy, isohexyloxy, 1-ethylbutoxy, 2-ethylbutoxy, 1,1-dimethylbutoxy, 1,2-dimethylbutoxy, 1,3-dimethylbutoxy, 2,2-dimethylbutoxy, 2,3-dimethylbutoxy, 3,3-dimethylbutoxy, 1-methyl-1-ethylpropoxy, 1-ethyl-2-methylpropoxy, 1,1,2-trimethylpropoxy, 1,2,2-trimethyl-propoxy, and cyclohexyloxy. Among these, more preferred lower alkoxy groups are linear or branched alkoxy groups having 1 to 4 carbon atoms. Particularly preferred is methoxy.

As n, 2 is particularly preferred.

Preferred examples of the aminothiazole derivative (I) useful in the practice of the present invention can include compounds in which R^1, R^2 and R^3 are the same or different and each independently represent a hydroxyl group or a linear, branched or cyclic alkoxy group having 1 to 6 carbon atoms, specifically a methoxy group or one of R^1, R^2 and R^3 is an amino, nitro or cyano group and the remaining two substituents are hydrogen atoms; R^4 and R^5 are the same and each represent an alkyl group having 1 to 6 carbon atoms, specifically an isopropyl

group; and n is 2. Illustrative of particularly preferred compounds are
N-(N',N'-diisopropylaminoethyl)-[2-(2-hydroxy-4,5-dimethoxy benzoylamino)-1,3-thiazol-4-yl] carboxamide,
N-(N',N'-diisopropylaminoethyl)-[2-(3-cyano-benzoylamino)-1,3-thiazol-4-yl]carboxamide, and
N-(N',N'-diisopropylaminoethyl)-[2-(3-aminobenzoylamino)-1,3-thiazol-4-yl]carboxamide.

Examples of the salt of the aminothiazole derivative (I), which is also useful in the practice of the present invention, can include inorganic acid addition salts, such as the hydrochloride, sulfate, nitrate, phosphate, hydrobromide and hydroiodide; and organic acid addition salts, such as the acetate, oxalate, malonate, succinate, maleate, fumarate, lactate, malate, citrate, tartrate, methanesulfonate and ethansulfonate. A preferred example of the salt is the hydrochloride.

The aminothiazole derivative (I) useful in the practice of the present invention includes various solvates such as hydrate.

The aminothiazole derivative (I) useful in the practice of the present invention can be prepared by the process disclosed in PCT International Publication WO96/36619 or WO98/17654.

In the present invention, the aminothiazole derivative (I) can be formulated together with a pharmaceutically acceptable carrier into a composition for oral administration or parenteral

administration. As compositions for oral administration, the aminothiazole derivative (I) useful in the practice of the present invention can be formulated into tablets, powder, granules or capsules by using suitable additives, for example, an excipient such as lactose, mannitol, corn starch or crystalline cellulose; a binder such as a cellulose derivative, gum arabic or gelatin; a disintegrator such as carboxy-methylcellulose calcium; a lubricant such as talc or magnesium stearate; and the like. Further, these solid preparations can be formed into enteric preparations by using a coating base such as hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate or a methacrylate copolymer. As compositions for parenteral administration, the aminothiazole derivative (I) useful in the practice of the present invention can be formulated into liquid preparations for injection, for example, by making combined use of water, ethanol, glycerin, a commonly employed surfactant and the like, or into suppositories by using a suppository base.

In the present invention, the dosage of the aminothiazole derivative (I) may range generally from 0.1 to 2,000 mg/day, preferably from 1 to 300 mg/day, notably from to mg/day in the case of oral administration although it varies depending on the age, weight, symptom, effects of treatment, administration method, and administration period. It is

preferred to administer this dosage in a range of from 1 to 3 times a day.

As the aminothiazole derivative (I) useful in the practice of the present invention have excellent colomotor enhancing effect and high safety as will be described subsequently herein, it is useful as a remedy for colonic motor dysfunction of mammals including human being. Illustrative of colonic motor dysfunction are irritable bowel syndrome, constipation, intestinal atony, and drug-induced motor dysfunction. It does not act on serotonin receptors or dopamine receptors [Gastroenterology, **116**(4) part 2, A1094, 1999] and different from conventional drugs, do not have side effects such as side effects on the central nerve system, e.g., extrapyramidal disorders and dizziness, and constipation as an excess effect.

Examples

The present invention will hereinafter be described in detail based on Examples. It should, however, be borne in mind that the present invention is not limited to the Examples.

[Pharmacological Test]

A description will next be made about a pharmacological test on certain aminothiazole derivatives (I) useful in the practice of the present invention. The followings are the compounds (test compounds) which were employed as test drugs:

(Compound 1)

N-(N',N'-diisopropylaminoethyl)-[2-(2-hydroxy-4,5-dim

ethoxybenzoylamino)-1,3-thiazol-4-yl]carboxamide trihydrate [Synthesized in accordance with the procedures of Example 38 of WO96/36619.]

(Compound 2)

N-(N',N'-diisopropylaminoethyl)-[2-(3-cyanobenzoyl-amino)-1,3-thiazol-4-yl]carboxamide hydrochloride [Synthesized in accordance with the procedures of Example 1 of WO98/17654.]

(Compound 3)

N-(N',N'-diisopropylaminoethyl)-[2-(3-aminobenzoyl-amino)-1,3-thiazol-4-yl]carboxamide [Synthesized in accordance with the procedures of Example 157 of WO96/36619.]

Test 1 [Effects on gastric and colonic motor activity]

Force transducers ("F-12IS", trade name; manufactured by Star Medical Technologies, Inc.) were chronically sutured in the gastric antrum and large intestines of male dogs (body weight: 9 to 11 kg, 5 to 6 dogs per group) (Itoh, Z. et al., Am. J. Dig. Dis. **22**, 117-124, 1977). Contraction signals from the respective regions in postcibal period were amplified and recorded ("RTA-1200", trade name; manufactured by Nihon Kohden Corporation). The contraction signals, which had been collected in a computer, were analyzed by using an analysis program ("DSSDDWHD V.30", trade name; prepared by Nihon Kohden Corporation), whereby motor indexes were calculated. The test

drugs were administered through catheters which had been chronically indwelled beforehand in the duodenum, respectively. Supposing that the coefficient of motor 30 minutes before the administration of drug was 100%, the results were calculated as percents of motor index until 1 hour after the administration. The results are presented in Table 1.

Table 1 Effects on Gastric and Colonic Motor Activity

Test drug	Dosage (mg/kg)	Percent of motor index	
		Gastric antrum	Large intestine
Control	-	91.8	98.1
Compound 1	10	163.7	136.1
Compound 2	10	189.5	221.7
Compound 3	10	244.6	249.9
Cisapride	1	158.7	114.5
Itopride	10	132.7	122.1
Mosapride	3	146.2	119.2

As is evident from Table 1, all the test drugs showed gastroprokinetic activity, but concerning colonic motility, cisapride, itopride and mosapride which are conventional drugs showed no significant effect whereas Compounds 1 to 3 which are compounds useful in the practice of the present invention exhibited marked enhancement of colonic motor activity.

Test 2 [Effects on defecation]

Test drugs were intraperitoneally administered to male SD rats (8 rats per group). Stools were recovered until 60 minutes after the administration, and their dry weights were measured. Supposing that that the average of stool weights in a control group was 100%, the averages of percent weights of individual test drug groups were calculated. The results are presented in Table 2.

Table 2 Effects on Defecation in Rats

Test drug	Dose (mg/kg)	Percent stool weight (%)
Control	-	105.6
Compound 1	10	361.8
Compound 2	10	766.7
Compound 3	10	733.3

As is apparent from Table 2, all the test drugs of Compounds 1 to 3 were confirmed to bring about a marked increase in stool weight. Incidentally, the conditions of those stools were all normal.

[Acute Toxicity Test]

ICR mice of 4 to 5 weeks old were used in groups, each consisting of 3 mice. The individual test compounds were separately suspended in a 0.5% methylcellulose solution and orally administered at 1,000 mg/kg, and the mice were observed

for 1 week. No case of death was observed in any of the groups administered with Compounds 1 to 3, respectively.

Preparation Example 1

Compound 1	20 g
Lactose	315 g
Corn starch	125 g
Crystalline cellulose	25 g

The above-described ingredients were combined into an intimate mixture, followed by the addition of a 7.5% aqueous solution of hydroxypropylcellulose (200 mL). The resulting mixture was formed into green granules through a screening of 0.5 mm in diameter. After the green granules were immediately rounded in a Marumerizer, they were dried into granules.

Preparation Example 2

Compound 2	20 g
Lactose	100 g
Corn starch	36 g
Crystalline cellulose	30 g
Carboxymethylcellulose calcium	10 g
Magnesium stearate	4 g

The above-described ingredients were combined into an intimate mixture. The mixture was formed into tablets of 200 mg/tablet by a punch of 7.5 mm in diameter by a single-punch tableting machine.

Preparation Example 3

Compound 1	100 mg
Sodium acetate	2 mg
Acetic acid	q.s. to pH 5.8
Distilled water	q.s. to 10 mL
	Total: 10 mL/vial

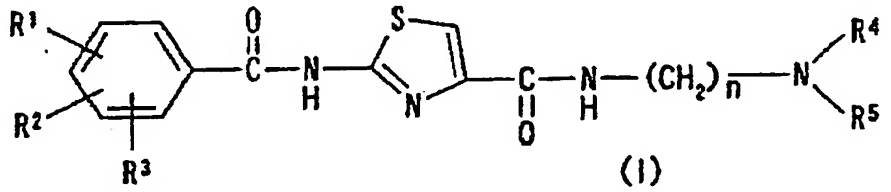
In accordance with the above formula, an injection was prepared in a manner known *per se* in the art.

Industrial Applicability

The aminothiazole derivative (I) useful in the practice of the present invention has excellent effect for improving colonic motor dysfunction and moreover, do not give side effect on the central nerve system via serotonin receptors or dopamine receptors. It is, therefore, useful as a remedy for irritable bowel syndrome, constipation, intestinal atony, drug-induced colonic motor dysfunction or the like.

CLAIMS

1. A colonic motor dysfunction remedy comprising, as an active ingredient, an aminothiazole derivative represented by the following formula (I) or a salt or hydrate thereof:



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wherein R^1, R^2 and R^3 may be the same or different and each independently represent a hydrogen atom or a hydroxyl, lower alkyl, lower alkoxy, amino, nitro or cyano group, R^4 and R^5 may be the same or different and each independently represent a hydrogen atom or a lower alkyl group, and n stands for an integer of from 2 to 4.

2. The remedy according to claim 1, wherein in the formula (I), said lower alkyl group is a linear, branched or cyclic alkyl group having 1 to 6 carbon atoms, and said lower alkoxy group is a linear, branched or cyclic alkoxy group having 1 to 6 carbon atoms.

3. The remedy according to claim 1, wherein in the formula (I), wherein R^1, R^2 and R^3 may be the same or different and each independently represent a hydroxyl group or an alkoxy group having 1 to 6 carbon atoms, R^4 and R^5 are the same and each represent an alkyl group having 1 to 6 carbon atoms, and n is 2.

4. The remedy according to claim 1, wherein in the formula

(I), one of R^1, R^2 and R^3 is an amino, nitro or cyano group and each of the remaining two substituents is a hydrogen atom, R^4 and R^5 are the same and each represent an alkyl group having 1 to 6 carbon atoms, and n is 2.

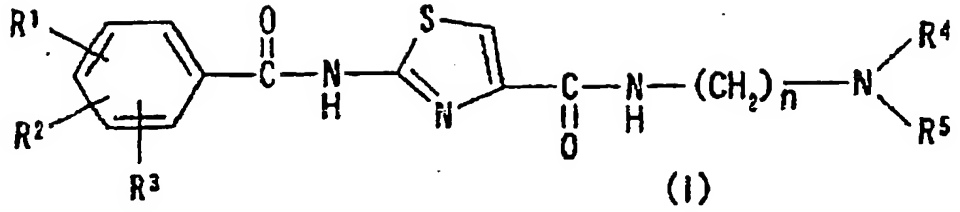
5. The remedy according to claim 1, which comprises as an active ingredient N-(N',N'-diisopropylaminoethyl)-[2-(2-hydroxy-4,5-dimethoxy benzoylamino)-1,3-thiazol-4-yl] carboxamide or a salt or hydrate thereof.

6. The remedy according to claim 1, which comprises as an active ingredient N-(N',N'-diisopropylaminoethyl)-[2-(3-cyanobenzoylamino)-1, 3-thiazol-4-yl]carboxamide or a salt or hydrate thereof.

7. The remedy according to claim 1, which comprises as an active ingredient N-(N',N'-diisopropylaminoethyl)-[2-(3-aminobenzoylamino)-1, 3-thiazol-4-yl]carboxamide or a salt or hydrate thereof.

8. The remedy according to any one of claims 1-7, wherein said colonic motor dysfunction is irritable bowel syndrome, constipation, intestinal atony or drug-induced colonic motor dysfunction.

9. Use of an aminothiazole derivative represented by the following formula (I) or a salt or hydrate thereof for the production of a colonic motor dysfunction remedy:



(I)

wherein R^1, R^2 and R^3 may be the same or different and each independently represent a hydrogen atom or a hydroxyl, lower alkyl, lower alkoxy, amino, nitro or cyano group, R^4 and R^5 may be the same or different and each independently represent a hydrogen atom or a lower alkyl group, and n stands for an integer of from 2 to 4.

10. The use according to claim 9, wherein in the formula (I), said lower alkyl group is a linear, branched or cyclic alkyl group having 1 to 6 carbon atoms, and said lower alkoxy group is a linear, branched or cyclic alkoxy group having 1 to 6 carbon atoms.

11. The use according to claim 9, wherein in the formula (I), wherein R^1, R^2 and R^3 may be the same or different and each independently represent a hydroxyl group or a linear, branched or cyclic alkoxy group having 1 to 6 carbon atoms, R^4 and R^5 are the same and each represent a linear, branched or cyclic alkyl group having 1 to 6 carbon atoms, and n is 2.

12. The use according to claim 9, wherein in the formula (I), one of R^1, R^2 and R^3 is an amino, nitro or cyano group and each of the remaining two substituents is a hydrogen atom, R^4

and R^5 are the same and each represent an alkyl group having 1 to 6 carbon atoms, and n is 2.

13. Use of N-(N',N'-diisopropylaminoethyl)-[2-(2-hydroxy-4,5-dimethoxy benzoylamino)-1,3-thiazol-4-yl] carboxamide or a salt or hydrate thereof for the production of a colonic motor dysfunction remedy.

14. Use of an active ingredient N-(N',N'-diisopropyl-aminoethyl)-[2-(3-cyanobenzoylamino)-1,3-thiazol-4-yl] carboxamide or a salt or hydrate thereof for the production of a colonic motor dysfunction remedy.

15. Use of N-(N',N'-diisopropylaminoethyl)-[2-(3-aminobenzoylamino)-1,3-thiazol-4-yl]carboxamide or a salt or hydrate thereof for the production of a colonic motor dysfunction remedy.

16. The use according to any one of claims 9-15, wherein said colonic motor dysfunction is irritable bowel syndrome, constipation, intestinal atony or drug-induced colonic motor dysfunction.

INTERNATIONAL SEARCH REPORT

Int[illegible]nal Application No
PC[illegible]P 01/03893

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/426 A61P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, MEDLINE, EMBASE, EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; June 1998 (1998-06) NOOR N ET AL: "Effects of cisapride on symptoms and postcibal small-bowel motor function in patients with irritable bowel syndrome." Database accession no. PREV199800351545 XP002185845 abstract & SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY, vol. 33, no. 6, June 1998 (1998-06), pages 605-611, ISSN: 0036-5521 --- -/--	9-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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